THE NATURAL HISTORY OF VESICULAR STOMATITIS

ROBERT P. HANSON[1]

Department of Veterinary Science, University of Wisconsin, Madison, Wisconsin

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I. INTRODUCTION

Although a counter trend exists, a great deal of the virus research of today is of the "hothouse" variety, to borrow a term from the horticulturist. The isolated virus is cultivated in an animal of convenient size and simple care, often an alien host to which the virus has been adapted and in which it is diligently studied. This diversion of our interest from the original to a model is the result of the complexity of the virus-host interaction in a free population. In consequence the investigators have been led to take a segment of the interaction, to dissect out, let us say, the immunological response of the host for closer study in the laboratory. The method of segmentation has been so successful in solving problems that we have become preoccupied with it and impatient with those who return to the wild disease to study the complex relationships that are inherent in large epizootics.

The clinician with his case reports and the veterinary and public health agencies which attempt to collect information on disease as it ebbs and flows

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across the globe are regarded all too casually from the laboratory. Investigators of viruses and viral infections, while critical of field reports, infrequently attempt direct observations of epizootics themselves. The scope of the problem is considered too great, and so the information which could be obtained is allowed to go by default.

> "Pasteur, often accused by his medical opponents of being merely a laboratory scientist, was always ready to move into the field when the work demanded it. . . . No fact appeared insignificant to Pasteur; he knew how to draw the most unexpected leads from the smallest detail. The original idea of the role of the earthworm in the dissemination of anthrax was thus born one day when we were walking through a field on the farm of Saint-Germain" (17).

The attitude of the research worker who places a higher value on observation made in a laboratory than on those made outside becomes more evident in textbooks. Reports of serological techniques, purification methods, vaccination procedures and disinfection rituals are usually adequately treated. Less effort is expended on the subject of distribution, dissemination and perpetuation of the virus. Information of this kind must be sought in periodicals put out by regional medical and veterinary societies, in reports of certain meetings, and even by solicitation.

This review resulted from such a search of obscure sources, and from utilization of replies to questions sent to officials responsible for control of animal disease. The information obtained by correspondence is marked in the text by an asterisk. The major purpose in writing this review has been to furnish a coherent account of the natural history of vesicular stomatitis. As a by-product the organization of the body of observations from field and laboratory led to certain conclusions that are at variance with the accounts found in most textbooks. The virus and the disease it produces are known by the name vesicular stomatitis (VS) only to students of virus disease and to disease control officials. The virus has served as a frequent model for the former. For example, Sabin (55, 56, 57) used it to study the development and mechanism of age resistance in mice; Sigurdsson (63) employed it in his investigation of the effect of environmental temperature on the susceptibility of the chicken embryo.

Officials charged with disease control (50) have been concerned primarily with the problem of differential diagnosis of vesicular stomatitis and foot-and-mouth disease. The latter has cost the United States millions of dollars. While in early stages the two diseases have been distinguished in the past only by animal inoculation tests, cattle suffering from vesicular stomatitis recover with few sequela, but those suffering from foot-and-mouth disease often become permanently impaired, or die. The policy of the United States government to stamp out foot-and-mouth disease when and wherever it appears in the United States, and to support this policy everywhere on the North American continent makes the early distinction of vesicular stomatitis and foot-and-mouth disease of obvious importance.

Farmers know vesicular stomatitis as a sore mouth of cattle, an unpredictable

disease that concerns them deeply only while it is present in their herd. The typical characteristics of its epizootics are probably illustrated by our own experience. An infectious stomatitis of cattle that swept through 3 large livestock areas in the United States in 1949 directed our attention to the disease. According to available records, the epizootic of 1949 began with a few scattered cases in the late spring. It became explosive in August, continued without diminishing through September and died out in October. Thousands of animals were affected and suffered loss of weight and temporary cessation of milk production. Although lesions of the mouth (figures 1 and 2), feet and teats indistinguishable from those of foot-and-mouth disease were often seen, the recovery was rapid and almost invariably without event or sequela. From

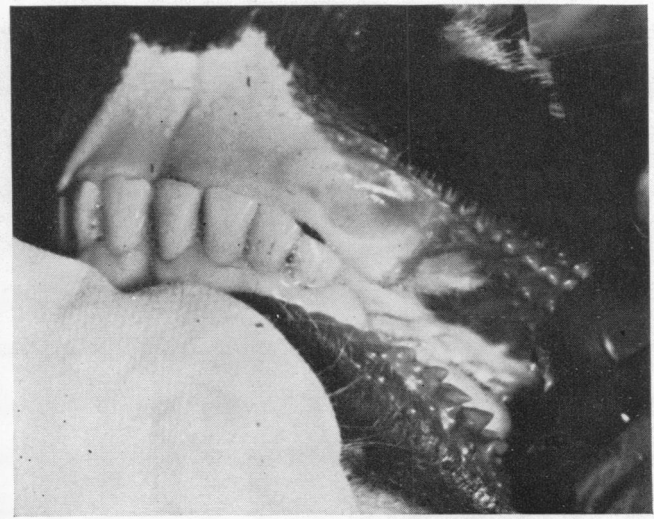

FIG. 1. Vesicle of the gingival mucosa of a cow, a specific lesion of vesicular stomatitis that develops within 18–24 hours after exposure to the virus.

infected cattle in 5 different states virus of the New Jersey type of vesicular stomatitis was isolated.

II. EARLY HISTORY OF VESICULAR STOMATITIS

Theiler (67) reported vesicular stomatitis as a disease of horses and mules in Transvaal, South Africa, in 1897 and referred to a prior outbreak in 1884. The infection appeared to be transferred by contact among animals having mouth abrasions. In the affected animals, elevated temperatures and loss of appetite were the first signs, followed closely by marked salivation. Vesicles appearing on the gums, tongue and lips quickly ruptured leaving reddish ulcerations which often coalesced. Within 6 or 7 days healing began, and complete recovery was quite rapid. Outbreaks of stomatitis have appeared in cattle of South Africa since 1897 particularly in 1934, 1938 and 1943 (5, 38, 72), but the causative agent or agents have not been identified and evidence that vesicular stomatitis virus was involved in any of them is lacking.

Although the disease may have disappeared from Africa before 1900, it has appeared and reappeared in America. The first established report of the disease in the United States was in 1916 (66). However, circumstantial evidence leaves little doubt that the disease was present earlier, and, in fact, it may have been carried to Africa from an unrecognized reservoir in the New World. Major General G. B. McClellan (39) in a letter to the Secretary of War describes a disease that suggests the presence of the virus of vesicular stomatitis among army horses during the Civil War.

"The artillery and cavalry required large numbers to cover losses sustained in battle, on the march and by diseases. Both of these arms were deficient

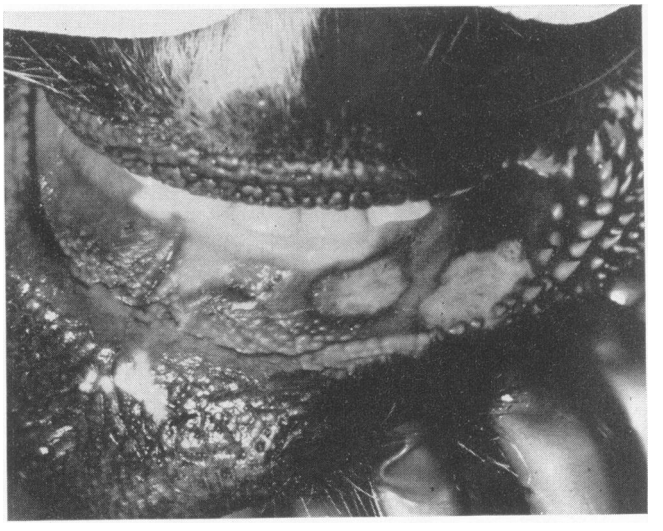

FIG. 2. Erosion of the gingival mucosa of a cow resulting from the rupture of a vesicle. The major portion of the epithelium of the tongue is sometimes lost in this manner.

when they left Washington (September, 1862). A most violent and destructive disease made its appearance at this time which put nearly 4,000 animals out of service. Horses reported perfectly well one day would be dead lame the next, and it was difficult to foresee when it would end or what number would cover the loss. They were attacked in hoof and tongues. No one seemed able to account for the appearance of this disease. Animals kept at rest would recover in time but could not be worked."

In 1904 J. R. Mohler (41) described a disease, occurring in summer and fall, which affected the mouths and feet of cattle in certain eastern and central western states. The initial signs were inability to eat, the formation of froth on the lips and dribbling of saliva. In the mouth small blisters appeared which quickly eroded and developed into ulcers which often coalesced. Sometimes swelling and painfulness affected the feet, fissures appearing around the coronet or in the cleft. In milking cows erosions occurred at times on the teats and extended to

the udder. The temperature rose for a short period and then recovery often took place in a week or 10 days. Mortality was less than 0.5 per cent. The disease was ascribed to eating of forage containing fungi or molds. However, Mohler (41) points out that he was unable to find the causative fungi or to reproduce the disease. It is difficult to find any significant way in which the disease described by Mohler differs from vesicular stomatitis whether it be clinical symptoms, course, or epizootiological factors. Concerning the epizootiology Mohler added,

> "The fact that this disease disappears from a locality at a certain time (winter) and reappears at irregular intervals would suggest the probability that certain climatic conditions were essential for the propagation of the causative "fungi" since it is well known that the malady becomes prevalent after a hot dry period has been followed by rain thus furnishing the requirements necessary—owing to this fact the disease is observed in one locality during one season and in an entirely different section another year, but reappears in the former center when favorable conditions prevail. In this way the affection has occurred at irregular intervals in certain sections of both the United States and Canada."

Mohler in his 1904 report mentioned an outbreak in Maryland and Virginia in 1889 and a recent outbreak in Texas.

Heiny (29) stated that cases of vesicular stomatitis occurred in western Colorado as early as 1906. Davisson recalled seeing stomatitis of horses in Chicago stock yards in 1907. The French (31, 46) diagnosed vesicular stomatitis in 1915 in horses arriving from America although there was no report of the infection in the United States that year. However, an outbreak of so called mycotic stomatitis was present then in cattle pastured in the Blue Ridge Mountains (43). The first symptoms were inability to eat, suspension of rumination and formation of froth on the lips. The mouth appeared red. Small blisters developed which later eroded and formed ulcers. The malady which did not prove to be a serious economic problem lasted through the fall.

III. EPIZOOTICS OF VESICULAR STOMATITIS

1. *Outbreaks during World War I.* While it is probable that vesicular stomatitis was present in America earlier, it was not until the 1916 outbreak that accounts appeared in the American veterinary literature (26, 30, 34, 42, 51, 66). The reports of the 1916 epizootic are worth considering in some detail. Infected horses were first seen August 16, 1916, in the Denver stock yards (36); these animals were isolated, and only a few infections, presumably secondary cases, occurred. The disease then was reported on ranches in the San Luis Valley, 300 miles from Denver, and in a logging camp where about 100 per cent of animals were infected. The ranches and the logging camp were widely separated, and possible means of transmission could not be found. Vesicles developed in both horses and cattle, and the disease was transmitted to both species by inoculation (18). Vesicular stomatitis appeared nearby in the remount horses congregated in

Ogden, Utah, and further north in remount horses assembled in Miles City, Montana (66). The fall round-ups in Wyoming contributed to the spread of the disease which occurred in cattle as well as in horses, the latter being affected more severely (21).

Eastward on the Great Plains, a few cases occurred late in the summer among remount horses congregated at Lathrop, Missouri, Grand Island, Nebraska (66), and in the stock yards at Des Moines, Iowa (26). Infected cattle as well as horses were seen in Kansas City, Kansas, and led to the suspicion of foot-and-mouth disease. The Bureau of Animal Industry lifted the quarantine when they demonstrated the transmissibility of the malady to both cattle and horses but failed to infect swine (18, 34). Even in November, 95 per cent of a small group of horses and some cattle exposed in Ft. Pierre, South Dakota, developed the disease (32, 51). Remount horses from points west and south passed through the Chicago and Calumet yards in Illinois in large numbers all fall. Only a few animals escaped the disease. On the nineteenth of October there were 500 cases of frank stomatitis among 4,054 horses in the Chicago yards (66).

Officers from the British remount depot in Newport, Virginia, published a report of their experience in 1916 (27). The disease appeared in the late summer at Newport and disappeared suddenly after 4 months. During that period several thousand cases of vesicular stomatitis were seen. It was a contagious, febrile disease affecting both horses and mules with the principal pathological changes confined to the tongue, buccal membrane, lips and occasionally the nose. Among the exposed horses 85 per cent appeared to be susceptible, of the large mules, 75 per cent and of the small mules, 25 per cent.

2. *Outbreaks in the western hemisphere.* A stomatitis among the American horses continued to plague the Allied forces in the fall and winter of 1917 (19*). No mention of the disease was made in America. Army records do not contain references to any cases from 1920 to 1922 but do mention 89 cases of stomatitis in 1924, the geographical locations of which are not given. Heiny (29) stated that a few infected animals may have been seen in Colorado during the 1917–1925 period but that an outbreak did not materialize during this time. In 1925 foot-and-mouth disease invaded Texas and the problem of differential diagnosis arose. A cow with both foot and mouth lesions easily confused with those of foot-and-mouth disease was demonstrated by inoculation of a horse to have vesicular stomatitis infection (13).

In 1925 a carload of young apparently healthy cattle arrived in Richmond, Indiana, from Kansas City. After reaching individual farms the animals developed lesions of the tongue and the mouth mucosa (13). Only cattle around Richmond were affected in the outbreak. The disease was transmitted to horses, and the infectious agent was isolated and preserved by animal transfer. It is now known as VS Indiana laboratory strain.

The following year a serious outbreak of vesicular stomatitis developed in New Jersey, beginning the middle of September and terminating about the middle of November (13). Some 752 diseased cattle were seen on 33 farms over a 300 square mile area; only 12 horses were infected. Cases with foot lesions

were observed, and milking cows in 2 or 3 herds developed lesions of the teats. It appeared that the milking itself possibly increased the degree of transfer and also increased the severity of the teat lesion. Cotton (13) observed that movement of infected and exposed cattle could account for only part of the spread of the disease. The New Jersey outbreak received considerable attention. Cotton also demonstrated the viral nature of the causative agent and its pathogenicity for cattle, horses and guinea pigs. The New Jersey virus was found to be immunologically distinct from the Indiana virus isolated the previous year. Since the disease induced was similar in both instances, the two viruses were considered to be two antigenic types, Indiana and New Jersey, respectively. Both type strains are still available for study, and all subsequent isolates have been found to be of one of these two serological types. An extensive outbreak occurred in Colorado 16 years prior to 1942 presumably in 1926 according to Heiny (29). Vesicular stomatitis was not seen or at least was not recognized for several years after 1926. A mycotic stomatitis of cattle was reported to have spread through parts of Virginia and West Virginia in 1934 and 1935 (44). Apparently no attempt was made to distinguish it from vesicular stomatitis.

In 1937 vesicular stomatitis appeared in Wisconsin (6), Minnesota (5*), eastern Dakota (2*), and Manitoba (14*). Both cattle and horses were affected, and far greater numbers were involved than in the New Jersey outbreak. The disease was first seen near the Minneapolis-St. Paul area in the late summer. It spread east into 8 counties of northern Wisconsin and northwest across Minnesota and into Dakota and Manitoba. The disease disappeared shortly after the first killing frost. In Manitoba it was observed (14*) that the disease was confined to livestock in wooded areas east of the Red River and along Lake Manitoba and Lake Winnipeg, and failed to spread to livestock on farms situated on the open plain.

Vesicular stomatitis also made its appearance in 1937 in Montana (30*) and West Virginia (9*). Fifteen of 30 horses were affected on a ranch in northern Montana. West Virginia had an extensive outbreak in cattle and horses particularly in the eastern part of the state. Since the virus was not isolated in 1937, it is not known whether the New Jersey or Indiana type virus was involved in these outbreaks.

Vesicular stomatitis was reported from South America for the first time in 1939 (4). An epizootic occurred among horses and cattle of the La Plata region of Argentine. Two years later, 1941, the disease broke out near Barinas, Venezuela, involving 716 cows, 195 horses and 48 pigs (3). This is the first account of the infection of swine with vesicular stomatitis virus.

During the autum maneuvers in Texas and Louisiana in 1941, vesicular stomatitis was reported among the 5,000 horses and mules engaged in the action (19*). Twenty-four cases were reported in September and 220 in October. The disease apparently spread to 3 other areas in Texas when elements returned to their posts. Army records reveal a total of 829 cases of stomatitis in 1941, 111 of which were diagnosed as stomatitis pustulosa infectiosa, and the remainder as vesicular stomatitis. According to the records of Kansas State College (16*),

the disease also appeared at Ft. Riley, Kansas, after the return of the horses from the Louisiana maneuvers to that post. The army report indicates that vesicular stomatitis was also present among civilian animals in Louisiana. Lauderdale (13*) writes that at least 8 cows in a herd in Lowndes County, Alabama, were infected in 1941. The disease diminished in Texas with the advent of cold weather and light frost (19*).

The Indiana type of vesicular stomatitis was isolated in Colorado in 1942 from an epizootic that occurred in September along the Platte River Valley over an area fifty miles long and twenty miles wide (29). Approximately three hundred horses and two thousand cattle were affected—almost half of the animals in the region. Swine did not show evidence of the disease. Teat lesions were seen in cattle. The 1942 epizootic in Colorado which began in September and terminated in November was the last time the Indiana type of vesicular stomatitis virus has been demonstrated in the United States.

The following year vesicular stomatitis again appeared in Colorado, but this time the virus isolated was of the New Jersey type and the region with affected cattle was in the western part of the state (29). About two hundred horses and two thousand cattle became diseased in Mesa, Delta and Montrose Counties at the junction of the Rio Grande and Gunnison Rivers. The outbreak developed in September as in the previous year. Sporadic cases also occurred in the Platte River Valley and in range cattle in Garfield and Eagle Counties. Lesions were observed on the feet and teats as well as in the mouth.

Vesicular stomatitis was reported in swine in Colombia in 1943 (54). It is now known that the disease is enzootic in Colombia, occurring every year with varying severity. The greatest incidence is during the dry months which are also those in which flies are abundant. The disease is most severe in cattle, but it also attacks horses and mules and, less frequently, swine. Only in the high mountain pastures are outbreaks of the disease rare or absent in cattle (18*).

In August, 1943, an extensive outbreak of vesicular stomatitis occurred in a hog cholera serum plant in Missouri involving half of the 1,500 swine in the plant (58, 59). The disease was severe and characterized by pyrexia, lameness and a few deaths. Virus of the New Jersey type isolated from the swine was similar to other New Jersey strains in the pathogenicity for cattle, horses and guinea pigs. Investigation did not reveal how the virus got into the plant, but within the plant the virus was apparently spread both by inoculation procedures used in hyper-immunizing swine, and by contact, the older and heavier swine showing the most severe reaction.

A severe epizootic of vesicular stomatitis that began in the latter part of July, 1944, in the same Colorado counties, Mesa, Delta and Montrose, where it had appeared in 1943 reached its peak in late September (29). Little or no rain fell throughout the period. The first cases were seen at the junction of the Colorado and Gunnison Rivers, and from there the disease spread in all directions infecting hogs and man as well as horses, mules and cattle. The manifestations were often severe, lesions appearing on all 4 feet of some horses. The report of human infection based on clinical evidences of 3 cases was the first in America

and the second in the literature. New Jersey type virus was isolated from both horses and cattle.

Vesicular stomatitis has been reported in swine on only 4 occasions: in Venezuela 1941, Colombia 1943, Missouri 1943, and Colorado 1944, all within a period of 4 years. The virus was isolated and typed in the Colorado and the Missouri outbreaks and was found to be New Jersey type in both. However, only in the Missouri outbreak was the isolation made from swine. Clinical evidence of the vesicular stomatitis in swine has not been obtained in any of the outbreaks of the disease occurring since 1944 although swine have been present on the same farms as infected cattle in many of these.

During an outbreak of vesicular stomatitis in 1944, 3 of 14 affected horses on a farm near Kerrville, Texas, manifested nervous disturbances which in one instance terminated in death (52). While the possibility of contributing factors was not eliminated, the signs observed resembled those induced by intracerebral inoculation of horses (20).

The first known outbreak in California was detected on April 23, 1945, in the Palo Verde Valley, an isolated area in the eastern part of Riverside County (11). Twenty-five animals in a herd of 130 dairy cattle showed vesicles or erosions of the tongue, dental pad and lip; a few had lesions of the udder. Body temperatures were as high as 107 F. Twenty-one infected places were found subsequently in the valley and were held under state quarantine until June 8, 1945. The second California outbreak apparently occurred independently the same spring at Bond's Corner near the southern border of Imperial Valley (11). Five infected premises were found, the first on May 16, 1945, and the last on June 5, 1945. Cattle and horses were involved in both outbreaks. Virus of the New Jersey type was isolated in both instances and sent to the Bureau of Animal Industry. In the summer of 1946, 3 cows were believed to have been affected with vesicular stomatitis in northern Idaho (26*). About 50 horses showed signs of infection in Arizona in 1947 (22*).

The joint Mexican-American commission for the control of foot-and-mouth disease, faced with the problem of obtaining accurate diagnosis of causes of stomatitis in cattle in 1947, developed isolation and complement fixation techniques for use on all suspected material (8, 11). For the first two years of its existence, 1947 and 1948, when techniques were being perfected, the data are sketchy. A single isolation of the Indiana type virus from the vicinity of Aguascalientes, Mexico, was made in 1947. Clinical diagnoses, however, indicated that the disease known for years as "mal de yerba" was vesicular stomatitis. Familiarity of the native farmer with the benign nature of this infection was one of the obstacles in developing the foot-and-mouth disease control program. In Mexico, vesicular stomatitis occurs throughout the year with the greatest incidence in the rainy season. In 1948 New Jersey type virus was demonstrated in Mexico and many clinical cases of vesicular stomatitis were seen. The disease was not reported from the United States. After about 10 years of smoldering activity vesicular stomatitis swept across the United States in 1949 from Mexico to Canada and from the Rockies to the Appalachians. The extent of the disease

in Mexico was adequately evaluated for the first time. One hundred and twenty-three isolations of vesicular stomatitis virus were made in Mexico by the Palo Alto Laboratories (23*). All but one isolate were of the New Jersey type; 98 of the isolations were from one state, Vera Cruz, where the single sample of Indiana type virus was also found.

The first appearance of vesicular stomatitis in the United States in 1949 was during May in Arizona where 50 cows of a herd of 141 were affected (17*). It shortly appeared in Texas where five hundred cattle and many horses had the disease (1*). New Jersey type virus was isolated from a horse at Jacksboro, in central Texas. The disease then appeared in three widely separated areas: the southeastern states, the upper Mississippi Valley and the Rocky Mountain States. In the southern area it was called mycotic stomatitis (6*, 24). The first cases were observed in late spring in Alabama, and the disease spread during the summer and fall over parts of Mississippi, Georgia, Tennessee, and Florida 12*, 24*). As the clinical symptoms were very similar to vesicular stomatitis, some clinicians diagnosed it as such. Apparently no attempts were made to transmit the disease or to isolate a virus; efforts to isolate a mold met with failure (24*). Although thousands of cattle were affected, the disease disappeared in the fall as did vesicular stomatitis in other areas.

The second center of infection was the upper Mississippi Valley. The disease appeared near St. Paul in June and spread slowly east and west until late July (5*). In August the disease swept eastward into 10 counties of northern Wisconsin (6) and northwestward across Minnesota into Manitoba (14*), which it reached in September; it died out in October. The counties in Wisconsin covered by the 1949 epizootic were for the most part the same as those that were concerned in 1937. Evidence of vesicular stomatitis was not seen in the intensive dairy country of southern Wisconsin during either outbreak. Most of the horses and many of the cattle in the epizootic area were affected in 1949, probably eleven thousand animals in Wisconsin, three thousand in Minnesota and five hundred in Manitoba.

The disease was often severe. Lesions appeared on the teats of two to ten per cent of the cattle and in the interdigital spaces of fifty per cent (6). The entire tongue epithelium sloughed off in some instances. The disease ran its course in 10 days producing considerable loss of weight and temporary loss of milk production in the affected cattle. A few human cases were reported among veterinarians and farmers in Wisconsin (28). The disease did not necessarily spread from an infected herd to the cattle on the adjacent farms (40) but appeared to skip across the countryside. In some herds all animals over a year old were affected and in others part of the cattle remained clinically unaffected although stanchioned with diseased animals. Animals were seen which drank from the same watering cup as diseased ones and yet remained unaffected. The virus isolated in Wisconsin was shown to be the New Jersey type (6, 12).

About the same time, further west, vesicular stomatitis appeared in Colorado, Utah, Wyoming and Montana. It was observed in Colorado in August and continued into October involving 65 herds of cattle and horses (29*). The

disease appeared in the Platte River region and extended into the mountains (11*). Rainfall was normal and insect populations were perhaps below normal. The Grand Junction Valley on the western slope was also involved. In Utah, New Jersey type virus was isolated from an outbreak among several hundred cows which occurred in October and November (20*). In Montana the epizootic developed in the fall among horses shipped from Texas (30*) and spread to other animals on the same farm. From a herd of 119 cows and 3 horses in Wyoming, where the disease did not reach until November, the New Jersey type virus was isolated (8*).

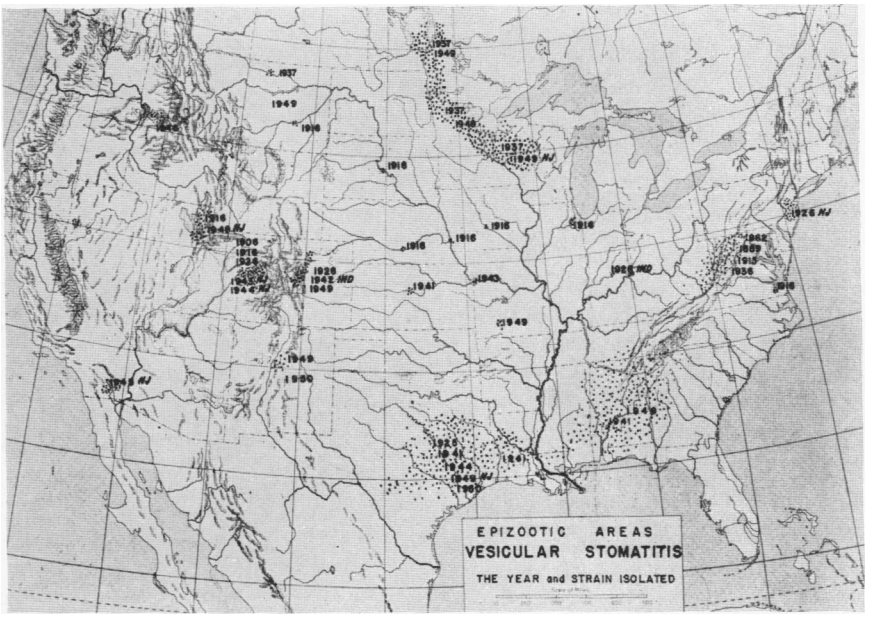

FIG. 3. Date and distribution of various epizootics of vesicular stomatitis in the United States and Canada.

Vesicular stomatitis continued to be prevalent in Mexico in 1950 (28*). Some 169 isolations were made, 124 cases being of the New Jersey type and 45 of the Indiana type. Eight states were involved; Vera Cruz from which 74 isolations were made was involved the most heavily.

In the United States sporadic cases were reported from Texas (1*) and New Mexico (27*). The disease was said to exist in Delaware, Georgia (12*) and Iowa (7*), but isolations and serological diagnoses were not made.

The geographical distribution of vesicular stomatitis in the United States and Canada is pictured in figure 3. The disease which is enzootic in certain countries bordering the Caribbean Sea—Colombia, Venezuela and Mexico—has repeatedly extended northward into Texas and the Gulf States. Epizootics have recurred in the Appalachian region, the upper Mississippi Valley and the Rocky Mountain region. Isolated outbreaks involving a few animals, often imported,

have appeared on the Great Plains. Vesicular stomatitis has not been recognized in the New England States, eastern Canada, the North Pacific States, British Columbia and Alaska.

3. *Outbreaks in the eastern hemisphere.* The first recognized appearance of vesicular stomatitis in Europe was during the first World War. The French veterinarians who examined shipments of American and Canadian horses in 1915 observed a transitory stomatitis characterized by blisters on the tongue and marked salivation (7, 33). Many army authorities blamed it on the moldy hay (31). Vigel (69) and Barrier (2) demonstrated the transmissibility of the disease by rubbing saliva from a sick horse on the tongue of a healthy animal. A stomatitis had been seen in 1915, 1916, and 1917 (2). Hundreds of horses were affected, the infection passing to French stock as well (69). A few cases were reported among cattle (16).

Vesicular stomatitis may have spread into other European countries, but unfortunately, the record is incomplete. English (9, 25), and Italian (45) investigators studied the disease. German references of that period to stomatitis of horses are generally to a form of horse pox although cases of "foot-and-mouth" of horses are described. The Irish irregularly have seen a stomatitis of cattle distinct from foot-and-mouth disease which is known as Armagh disease. The condition appeared to resemble vesicular stomatitis less than it did erosive stomatitis (21*). Vesicles have never been observed and horses are apparently insusceptible, but critical differential studies have never been made.

Vesicular stomatitis has not been described in available veterinary publications from the Orient. A former member of the Chinese veterinary service, a branch of the Bureau of Agriculture and Forestry, expressed the opinion that vesicular stomatitis might be present in China (3*). Stomatitis of unknown etiology is not uncommon in horses. Vesicular stomatitis was reported in a U. S. Army horse in the China-Burma-India theater in 1944 (19*). Outside of North and South America where the disease is enzootic and possibly Asia where it also may be enzootic, vesicular stomatitis has appeared as a transient epizootic occurring in Africa twice, 1884 and 1897, and in Europe extending on one occasion over a 3 year period, 1915, 1916 and 1917 (see figure 4).

IV. EXPERIMENTAL STUDIES OF VESICULAR STOMATITIS

1. *Role of host.* a. *Host range.* Clinical manifestations of vesicular stomatitis have been seen in cattle and horses in many localities over the past ninety years. Early accounts emphasize the disease in horses (16, 27, 66); recent accounts, in cattle (6, 29). This apparent shift in host specificity may be due in part to the decrease in the numbers and value of horses which has focused attention on cattle, and in part to the development of improved virological procedures (6, 10, 23, 53). The latter makes it possible to distinguish accurately vesicular stomatitis of cattle from foot-and-mouth disease. Diagnoses of cases of vesicular stomatitis are now made which formerly would have been indistinguishable from and considered clinically as foot-and-mouth disease.

Infection of swine has been reported twice in South America and twice in

the United States, isolation from swine being made in one of the latter instances (58). The infrequency of the disease in swine is rather remarkable considering the susceptibility of this species experimentally to inoculation by the cutaneous, intravenous or intracerebral injection routes (35, 60). Wagener (71) transmitted VS among young pigs by contact. Furthermore, the quantity of virus necessary to produce an infection in swine is not greater than that required in cattle. Refractivity appears to depend upon unknown epizootiological factors.

Early reports of human infections were based upon clinical findings and suggestive association (9, 29). More recently, serological evidence of vesicular stomatitis virus infection was associated with a clinical entity in Wisconsin (28). The disease may be more prevalent among people handling animals in

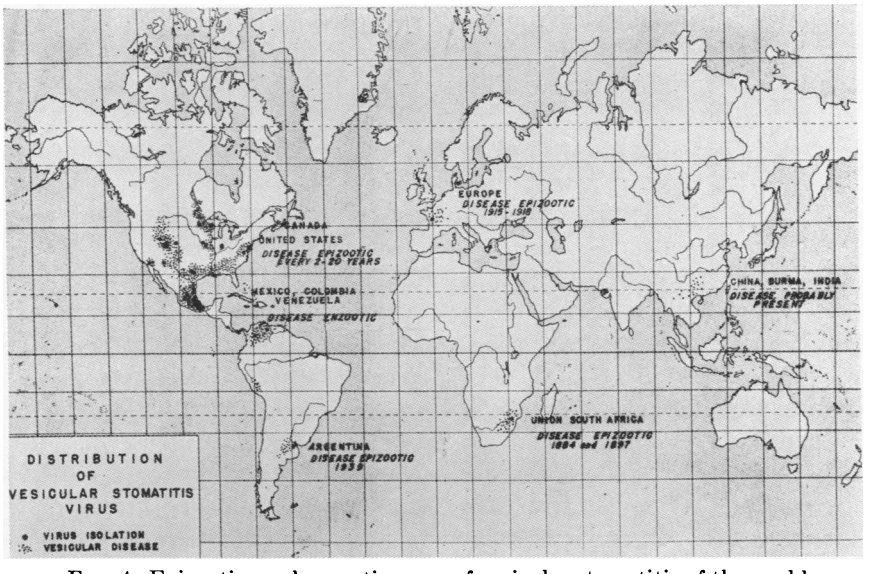

FIG. 4. Epizootics and enzootic areas of vesicular stomatitis of the world.

times of epizootics than had been supposed since definitive diagnosis depends upon laboratory procedures. Although virus was not isolated from the Wisconsin patients, it was from a cutaneous form of the disease in man (25*). In the latter instance accidental injection of the finger of a worker at the Palo Alto Laboratory in Mexico with known New Jersey type vesicular stomatitis virus resulted in the development in 48 hours of a large vesicle 3 cm long. Fluid from the vesicle caused foot pad lesions in guinea pigs typical of vesicular stomatitis. The vesicle on the finger healed in 10 days. A fatal encephalomyelitis was induced in monkeys (*Macacus* and *Cynomologus*) by the virus when it was introduced intracerebrally, but inoculation of the skin of the hand did not result in a response (65).

Infection of sheep and goats, if it occurs at all, is rare. Three groups of investigators (13, 35, 61) failed to produce a clinical disease in sheep by inoculation of virus on the tongue or gum, but a fourth (71) reported success. Vesicular

stomatitis has been diagnosed clinically in sheep (23*). Since some sheep appear to possess normal virus-neutralizing substances in the serum, and since other diseases produce stomatitis lesions in sheep, only isolation of the virus should be considered as evidence of infection (35). The susceptibility of deer (10*), peccary and antelope is completely unknown although the possibility remains that they may serve as reservoirs of the infection.

Heiny (29) and McDermid (40) each reported a dog with lesions of the tongue in an epizootic area. Neither isolation nor serological evidence of infection was obtained. Dogs have been refractory to experimental infections (35). One carnivore, the ferret, was highly susceptible to several routes of experimental infection including nasal instillation (35). Many rodents are readily susceptible. Virus introduced by the intracerebral route usually proved fatal to mice (15, 49), hamsters (35), guinea pigs (14, 49), rats (49), and chinchillas (35). Intradermal injections induced foot pad lesions in guinea pigs and wild rats (70, 71). Young mice, chinchillas, and ferrets succumbed to a fatal pneumonia following nasal instillation (35, 48).

The degree of resistance of most species of animals to infection with vesicular stomatitis virus does not remain the same throughout the life of the individual. In cattle the adult appears to be more susceptible than the calf. Field observers have seldom seen cattle less than one year old with typical lesions of the disease (29, 40). Experimentally, calves may be infected, but the thermal response is often biphasic and the disease milder than observed in mature animals. Foot pad lesions are larger and are produced more consistently in mature than in young guinea pigs (35). Sigurdsson (62) observed that with increasing age the chicken embryo becomes less susceptible to the virus. Young animals, on the other hand, are more susceptible to invasion of the central nervous system with fatal results (55, 56). Invasion of the central nervous system by the virus was a constant result of experimental inoculation by almost any parenteral route in mice less than 3 weeks of age. Refractivity to clinical infection by any route other than intracerebral increased from almost none to completeness in mice between the fourteenth and thirty-fifth day (55).

In summary, then, it appears that the natural host range of vesicular stomatitis is much more restricted than the experimental host range. The virus has been isolated from only 3 species although 10 are known to be susceptible to infection. There is a possibility that unrecognized mild infections exist among some animal species and constitute a reservoir of the virus.

b. *Immunity.* Following infection with vesicular stomatitis virus, specific immunity of short duration develops in cattle. Within thirty to sixty days after recovery from the disease many animals can be reinfected experimentally with the same strain of virus with clinical stomatitis resulting. These animals possess at the time of reinfection significant titers of antibody as determined by the ability of their serum to neutralize virus in embryonating eggs (35) or to act in the complement fixation test (10). Usually, even the circulating antibody has disappeared from field herds within 6 months (6). With an ephemeral immunity the susceptible population is not reduced in successive years. It ap-

pears that the number of carriers must be extremely rare or enzootic foci would be more common. As far as the size of the susceptible population is concerned, vesicular stomatitis could sweep across the country every summer.

c. *Density of susceptible population.* The distribution of susceptible species appears to have been a minor influence in the spread of vesicular stomatitis. The heaviest populations of cattle and horses often have escaped, the virus spreading instead through scattered populations. The Wisconsin-Minnesota-

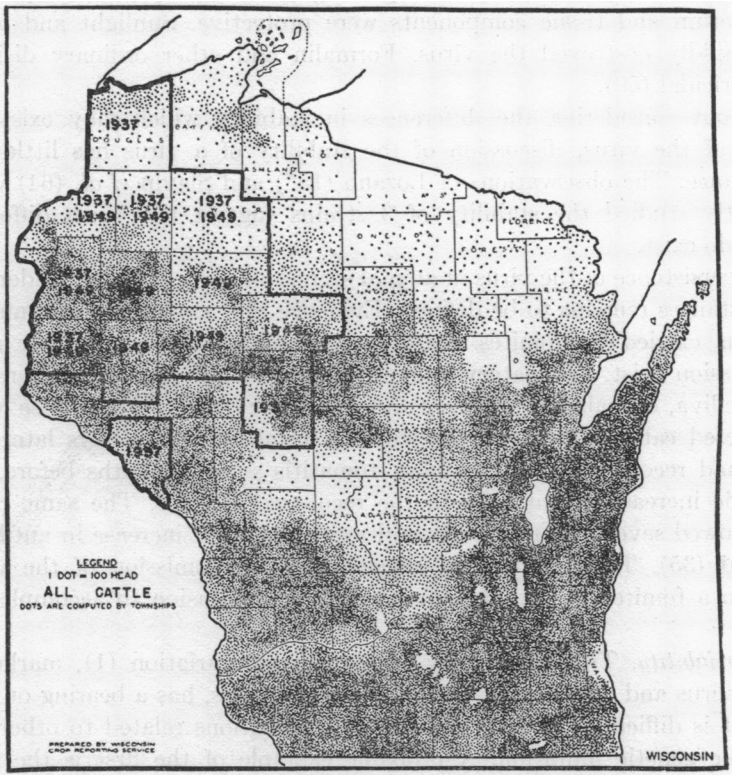

FIG. 5. Prevalence of vesicular stomatitis in 1937 and 1949 in relation to the cattle population of Wisconsin. (Data on the 1937 epizootic are incomplete.)

Manitoba outbreak in 1949 covered almost exactly the same territory that was invaded in 1937. On both occasions the heavy cattle population to the south in Minnesota and Wisconsin was left untouched. As can be seen in figure 5, the spread of the disease was not centrifugal but rather along a restricted path.

2. *Role of the virus.* a. *Physical stability.* Certain properties of a virus, physical stability in particular, often have a direct bearing on the transmissibility of the virus and consequently its epizootiology. At body temperature of man, 37.5 C, the New Jersey type virus Wisconsin strain remained active for 3 to 4 days in allantoic fluid (68). At refrigerator temperatures of 6–8 C the virus retained its titer for a week or more and its infectivity could be demonstrated for 6 to 8

weeks. Olitsky and his associates (50) demonstrated infectivity of vesicular stomatitis virus in guinea pig vesicles buried in garden soil at 4–6 C for 31 days. Frozen at −10 to −15 C the virus was preserved for months with little change. The hydrogen ion concentration of the suspending medium had considerable effect on the viability of the virus in studies at 37 C, a phosphate medium at an acid pH of 5.6 hastened the destruction whereas a phosphate medium at an alkaline pH of 7.8 preserved the activity (15*). Sodium chloride (0.85 per cent) was harmful to the virus, the activity being lost in 21 days when kept at −20 C (3*). Serum and tissue components were protective. Sunlight and ultraviolet light rapidly destroyed the virus. Formalin and other ordinary disinfectants were viricidal (50).

Without considering the differences in stability which may exist between strains of the virus, discussion of the stability of a virus has little practical significance. The observations of Lozano (15*) and Slavin *et al.* (64) who independently studied the stability of 3 strains suggest that such differences in strains do exist.

The persistence of the virus in animal secretions and excretions under different circumstances remains to be defined. Evidence that cattle may become infected by virus carried by fomites is usually complicated because other means of transmission exist. Laboratory studies suggest that the virus can persist in infected saliva, on pails, on mangers and in hay for 3 to 4 days. A nose lead, used on infected cattle and then used without disinfection two days later on cows which had recovered from vesicular stomatitis several months before, induced a specific increase in antibody in the recovered animals. The same procedure was followed several months later and again a specific increase in antibody was observed (35). This observation suggests that transmission of the virus can occur on a fomite capable of inducing sufficient abrasion to accomplish inoculation.

b. *Variability.* The potentiality of a virus for variation (1), marked in influenza virus and apparently lacking in mumps virus, has a bearing on epizootiology. It is difficult to separate the pseudo-variations related to other changes from true genetic mutation. A probable example of the first is the apparent greater infectiousness of vesicular stomatitis virus for cattle in recent years, an increase which may well be a result of a change in emphasis on the part of the observer arising from the increased numerical and economical importance of cattle as compared to horses.

Vesicular stomatitis of cattle is produced by 2 serologically distinct viruses. Although the names of viruses have been fabricated by man generally on the basis of an isolated experience, they often exert undue influence on our ideas of taxonomic relationships. For example, would the New Jersey and Indiana strains of vesicular stomatitis virus have been considered as 2 serotypes of one virus if one strain had been originally isolated from horses and the other from swine? If this situation had obtained, it is likely that the pathologic relationship of the two agents would have been recognized eventually after the agents had received distinct names. Such a chance, however, would have led to greater care

in distinguishing the properties of the two agents that too often are bracketed together without sufficient evidence.

The New Jersey and Indiana serotypes of vesicular stomatitis virus differ in properties other than antigenicity. The New Jersey strain has appeared to be in definite ascendency during recent years and has been frequently isolated. The Indiana virus has been obtained only once in the United States since the original isolation in 1925. In Mexico during 1949 (28*) a single culture of Indiana virus was obtained in contrast to 122 cultures of New Jersey virus. The pathogenicity of several isolates of New Jersey strain virus has been shown to be greater for susceptible animals than those of Indiana strains. Foot lesions have been seen only among cattle affected with New Jersey type virus (13, 29). Experimentally, a New Jersey strain when introduced into the brains of cattle produced paralysis and death; cattle inoculated with an Indiana strain experienced a rise in temperature and recovered (20). Passage of a New Jersey strain isolate in brain tissue culture medium resulted in increased neuropathogenicity. Similar cultivation of an Indiana strain isolate caused no change (47). Both agents, however, infect the same species of animals and produce similar lesions. Their particle size on the basis of filtration through gradocol membranes is about 70–100 millimicrons (22, 37).

Isolates of either serotype of vesicular stomatitis virus have been studied only superficially for differences in properties. Two strains of New Jersey serotype, Wisconsin and Missouri, have been found to differ markedly in their pathogenicity for ferrets, and also to differ in the time required to induce foot pad lesions in guinea pigs (29). The delay characteristic of the Wisconsin isolate was sometimes as long as 8 days beyond the usual 2 days incubation period. On the other hand, an Indiana isolate C was similar to the Wisconsin isolate in ferret pathogenicity. Variant strains of virus have resulted from prolonged passage in embryonating eggs, in mouse brains (49) and in tissue culture (47). Eichorn and Manthei (19) reported greater virulence for embryos after passage in that host and Galloway and Elford (23) observed that egg adapted virus could be filtered more easily through gradocol membranes passing an average pore diameter of 13 rather than 14. Sigurdsson (62) found the virus after 60 passages in chicken embryos to be still fully virulent for mice, and the pathogenicity of the virus for the embryo to be unchanged. Passage in mice by intracerebral inoculation and in cultures of brain tissue (47) has resulted in selection for neurotropism, as indicated by a shorter incubation time of the variant.

c. *Association with other organisms.* Other infectious agents may have an effect on the pathogenicity of vesicular stomatitis virus. Shahan (61) observed that simultaneous injection of swine with hog cholera virus and vesicular stomatitis virus resulted in a delay or absence of vesicular lesions. Vesicular stomatitis virus and foot-and-mouth virus simultaneously injected into eggs significantly prolonged the survival of the foot-and-mouth virus (23); the vesicular stomatitis virus grows readily in this organism but the latter does not. Reports of dual infections of cattle with vesicular stomatitis virus and foot-and-mouth virus have not been encountered. Since the usual method of differential diagnosis would

not distinguish dual infections from infections produced by vesicular stomatitis virus alone (23, 50) or foot-and-mouth virus alone (59), the absence of such reports is not surprising. An interaction of considerable economic importance is the tendency of vesicular stomatitis infection to predispose the bovine udder to bacterial invasion with streptococci (6, 29).

A problem of differential diagnosis has existed and still exists between vesicular stomatitis and both foot-and-mouth disease and so-called mycotic stomatitis. This problem can be resolved between the first two diseases by serological tests. On the basis of signs, lesions, course and epizootiology of the disease it is not possible to distinguish vesicular stomatitis and the so-called mycotic stomatitis. Since a causal relationship between fungi and mycotic stomatitis has not been shown (41), bovine stomatitis of unknown etiology could be termed more correctly: sporadic ideopathic stomatitis.

Differential diagnosis of vesicular diseases in swine was tremendously complicated in the summer of 1952 by the first appearance of vesicular exanthema outside of the West Coast where it had existed as an enzootic for two decades. The clinical manifestations in swine of foot-and-mouth disease, vesicular exanthema and vesicular stomatitis are so similar that animal transmission and serological procedures are necessary for their differentiation. Foot-and-mouth disease attacks swine and cattle, vesicular exanthema, swine and sometimes horses, but vesicular stomatitis attacks all three species. The diseases are caused by viruses of which there are 3 serotypes of foot-and-mouth disease, 2 of vesicular stomatitis and as many as 6 of vesicular exanthema. Both vesicular exanthema and foot-and-mouth disease have been transmitted by feeding infected garbage to hogs. Whether this is the usual means of dissemination is unknown.

3. *Role of the environment.* a. *Seasonal incidence.* A historical account of vesicular stomatitis outbreaks establishes the relationship between the disease and certain seasons of the year. In the United States the disease has been limited to the summer and fall season, epizootics developing only in July, August, September, and October, the greatest number of cases occurring in September. Arrival of heavy frosts in October or November is usually followed by cessation of an outbreak within a week or two. Only a few questionable cases have been reported in the winter and early spring months, and the virus has never been isolated during these months of the year. However, cattle have been found to be readily susceptible to inoculation throughout the winter (35). (See figure 6).

b. *Topography and climate.* Not only is there an apparent relationship between climatic zones and frequency of occurrence of vesicular stomatitis, but it appears that limitations are imposed on the spread of the disease by certain physical features of the land or by habitat conditions within these zones. The disease has occurred both east and west of the Great Plains, but within that area the cases have been restricted to stock yards (16*, 26, 30*, 51, 66). Vesicular stomatitis spread rapidly in certain valleys of the Rocky Mountains (29), in the upper Mississippi Valley (6), and probably in the southeast coastal region. The highly contagious disease as it occurs in the upper Mississippi Valley is quite in contrast to the self limiting disease of the Great Plains. Lay (14*) reported

that the disease as it occurred in Manitoba in 1937 spread readily among cattle pastured in the woodland of the lake region but failed to make headway on the open plains. The disease has repeatedly spread along two waterways in Colorado, the North Platte and the Gunnison Rivers (29). Only scattered cases have occurred in other areas. Woodland pastures, rivers and lakes are common in most of the epizootic regions and absent in the regions where the disease is self limiting.

c. *Periodicity.* The incidence from year to year has varied according to the region. In the frostless area the disease is encountered every year. As one proceeds further north in North America or south from the Caribbean region in South America, the disease appears less frequently. In the southwestern United

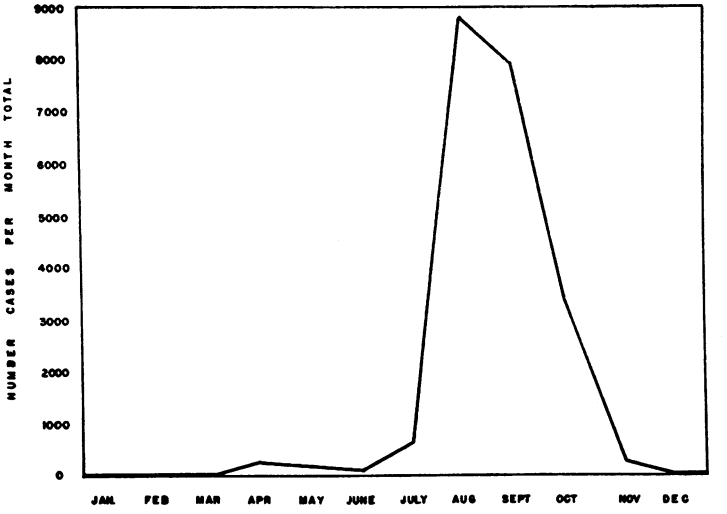

FIG. 6. Prevalence of vesicular stomatitis by month on estimates covering a 30 year period.

States, vesicular stomatitis has been seen every few years; in the north central states, once or less during every decade (figures 3 and 7).

d. *Transmission.* Theiler (67) first pointed out the difficulty encountered in attempts to produce infection by contact. The disease was seldom transmitted to normal horses watered from the same bucket with diseased animals unless frank abrasions were present on the lips of the normal horses.

Other workers have reported irregular results. Cotton (13) exposed within a small enclosure 4 cows and one calf to several infected cattle whose vesicles ruptured during the exposure. Three of the cows developed the infection. Two other cows exposed by direct contact to a diseased animal 5 days after rupture of the vesicles had occurred were not infected. Four cows which were stabled in stalls next to sick animals and which ate hay moist with diseased saliva did not become infected. Olitsky *et al.* (50) infected 3 of 6 cows by contact. Neither of these workers cited the role of mouth abrasion as stressed by Theiler. Wagener (71) failed to transfer vesicular stomatitis by contact of infected cattle with noninfected calves or infected calves with normal cattle.

In our experience two susceptible cows stabled side by side and drinking from common buckets with two infected animals did not become diseased. Neither clinical signs nor specific antibodies were produced. The principals were later shown to be susceptible by injection of the oral mucosa. Virus infective for cattle failed to produce lesions in the mouth of two cows although swabs moistened with virus were rubbed over the tongue and lips. These cows were susceptible as determined by later injection. An aerosol of vesicular stomatitis virus did not induce mouth lesions in a cow which was exposed to it, but this animal developed neutralizing antibodies and was refractive to injection. Vesicular stomatitis with typical lesions of the mouth, salivation, and pyrexia was induced only by intracutaneous inoculation of the tongue and gum or by rubbing virus over an abraded mucus surface.

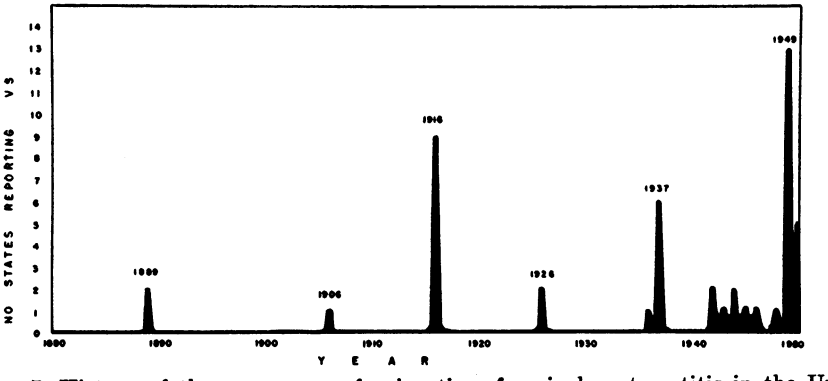

FIG. 7. History of the occurrence of epizootics of vesicular stomatitis in the United States. The peaks are only roughly indicative of the number of animals infected since the numbers of animals are not proportional to the population reported by the states. Obviously smaller outbreaks have been forgotten with time and the major ones have diminished in relative importance.

Transmission of the disease within a herd or between animals in adjacent herds with the production of the clinical disease would require not only the transfer of virus as in infected saliva but also the introduction of the virus beneath the mucosal surface of the mouth. Theiler (67) pointed out that this can be accomplished naturally by feeding contaminated rough forage capable of inducing abrasions sufficient to allow penetration of the virus. Abrasions or cuts produced by other means such as biting insects should accomplish the same result.

V. DISCUSSION AND CONCLUSIONS

Several characteristics of vesicular stomatitis epizootics have been reviewed from the historical and experimental point of view. Now we can ask, how is the virus of vesicular stomatitis perpetuated and spread?

If vesicular stomatitis virus is capable of living only a few days in barns, as it appears, it must be kept alive by continuous passage from one susceptible

animal to another. Certainly if all active cases of the disease were to disappear for one month, it is unlikely that the disease would reappear. An annual hibernation of the virus for several months, i.e., the period from November to June, during which the virus persists only on fomites is extremely unlikely. It would be much more reasonable to look for the source of the virus in the infected animals of some area where the disease spreads without interruption or to a silent reservoir in an area where the disease occurs at frequent intervals.

So far as we know vesicular stomatitis has appeared in Canada not more than once every decade and in the United States at irregular intervals, ranging from very infrequently near the northern border every 10 to 30 years, to much more frequently along the southern border usually 1 to 10 years. Evidence is lacking that would suggest the occurrence of vesicular stomatitis in the United States every year. Records of the United States-Mexican Commission for control of foot-and-mouth disease indicate that vesicular stomatitis exists in Mexico throughout the year. Semitropical America thus would appear to be the logical origin of most outbreaks of the vesicular stomatitis. Cattle alone could be the reservoir in those areas, the disease being perpetuated by intermittent transfer from herd to herd. A survey of the cattle in Mexico might show the plausibility of this suggestion.

It may be assumed that the severity of the manifestations of the disease varies in cattle in the enzootic areas, some infections being silent and unrecognized. Mild infections can be induced by experimental exposure of cattle to the virus by nebulization. The virus multiplies and antibodies are induced, but signs of disease are absent. Serological studies in convalescent Wisconsin herds indicated that such mild infections can occur naturally. All individuals in a herd of 26 studied in 1949 possessed specific antibodies one month after natural infection although the disease was observed in only 50 per cent of the animals. Certain wild animals may augment the cattle reservoir or even serve as the primary source of infection. Little can be concluded until the immunological status of deer, peccary, sheep, and certain other mammals is investigated.

Three aspects of the epizootiology of vesicular stomatitis are suggestive of a vector transmitted disease: (a) the seasonal incidence; (b) the ecological limitation; and (c) the rapidity and manner of spread.

The disease appears in summer and disappears shortly after insect killing frosts. The disease has often but not always failed to spread along lines of commerce such as roads. Rather, it follows natural waterways, sparing adjacent farms away from the water and infecting distant herds along the waterway. Epizootics generally occur in regions where cattle are pastured in woodland where streams or lakes are common rather than on open plains. The former provides conditions characteristic of the habitat requirement of certain insects.

What vector might satisfy these requirements? A number of genera of diptera—stable flies, horse flies, black flies and mosquitoes are abundant during the summer and fall. All are possible vectors. The distribution of biting insects depends primarily on availability of the habitat required by their larval stages, and secondly on the flight range of the adult. The larvae of the stable fly, *Stomoxys*

calcitrans, and the horn fly, *Lyperosia irritans*, develop in decaying organic material. The stable fly ranges over almost the entire continent, but the nose fly is most prevalent on the great plains. The stable fly would be suspect; the horn fly would merit little investigation. Mosquitoes, horse flies and black flies, which spend their immature existence in water and are rare in dry regions, fit the description most closely.

The biting preference of the diptera are not well known. Some species of mosquitoes feed on a wide assortment of animals, others restrict themselves almost entirely to a single species. Horse flies or tabanids bite horses, cattle and man but seldom attack swine and birds. Preference may depend partially on species factors but also on the availability of blood to attack from the exterior surface. The thick skin and blood-scarce fat layer which underlies the skin on the hog probably are major reasons why so many insects fail to attack these animals. The site of feeding might be of considerable importance in the transmission of a virus like vesicular stomatitis. Observations, in June and July of 1952, revealed that mosquitoes tend to bite about the lips of cattle and horses more than do horse flies or deer flies.

The prevalence of insects varies from season to season probably for reasons of rainfall and unseasonable freezing weather. The biting attack of adults can be reduced in the case of horse flies or increased in the case of mosquitoes by the amount of cloudy weather or reduced in both instances by cold weather.

On the basis of the factors mentioned, the horse fly could be a vector. The prevalence of tabanids in Wisconsin closely approximates the extent of the 1937 and the 1949 epizootics. Tabanids are found in other epizootic areas, usually in large numbers, and are relatively rare in some of the regions such as the Great Plains which have so far escaped a general attack. The incidence of vesicular stomatitis in Colombia is greatest during the tabanid season. Certain species of mosquitoes are also peculiar to these regions, and their seasonal abundance more closely approximates the case prevalence of vesicular stomatitis than does that of the tabanids which are usually most abundant in June.

The critical experiment remains. Can vesicular stomatitis be transmitted experimentally by insects such as horse flies or mosquitoes, and can the virus be isolated from wild insects during an epizootic? Recently, the first has been accomplished in preliminary experiments. If the second question can be answered, our understanding will be greatly increased.

Assuming that a reservoir of vesicular stomatitis exists in tropical America and that an insect can transmit the virus, the question arises as to how the virus can travel north two to three thousand miles in five months or less. Several possibilities may be suggested: (a) movement of infected cattle along sales routes, and (b) a migration of reservoir animals. The first has occurred repeatedly. The earliest cited example was the procurement of western horses in 1916, assembling them at remount depots in the Middle West, and shipping them east to the Atlantic coast and to Europe.

The Indiana outbreak in 1926 appeared on farms receiving cattle of a single importation from Missouri (13). In 1949 vesicular stomatitis broke out at a Montana ranch after introduction of a horse from Texas (30*). Shipment of

animals may spread the disease about the country creating new foci of infection. Abortive epizootics have occurred in some areas and fulminated outbreaks in others depending on the local conditions and possibly on vectors. Under these conditions chance would determine to a great extent where and when outbreaks might occur. Should we consider Mexico to be the immediate source of virus, the contiguous states, Texas, New Mexico, Arizona and California, might be expected to have the greatest traffic from infected areas and the best chance of having frequent outbreaks. This does not mean that cattle would have to cross the Rio Grande. If cattle from southern Mexico were shipped to Matamoros on the Rio Grande, the disease could quite likely cross the river and infect cattle in Brownsville, Texas, which may in turn be shipped north. The farther the distance from the frostless regions the lesser the chance of initial infection, e.g., in Minnesota outbreaks occurred 12 years apart and in Montana 21 and 12 years apart.

Another means by which virus of vesicular stomatitis could reach such northern areas as Minnesota would be by migratory animals such as birds. Fowls and pigeons have been completely refractory to experimental infection. Since the virus seems to prefer mammals with lower body temperature, i.e., 97 to 101 F, it seems unlikely that birds could become infected and carry the virus except mechanically (35). Among mammals only the bat has sufficient range to migrate from Mexico to Minnesota; its susceptibility is unknown.

In summary it is postulated that vesicular stomatitis spreads north each season from an enzootic area in tropical America sometimes travelling only a short distance and at other times sweeping north almost to the limits of the cattle raising country. The introduction of initial cases into certain areas, such as the upper Mississippi Valley, sets up a rapidly spreading epizootic, presumably dependent upon an insect vector. In the absence of this vector the disease is self limiting.

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COMMUNICATIONS

1*. BOUGHTON, I. B. 1951 Texas A. and M., College Station, Texas.
2*. BRANDENBURG, T. D. 1951 State Veterinarian, Bismarck, N. D.
3*. CHOW, T. L. University of Wisconsin, Madison, Wisconsin.
4*. DAVISSON, L. 1951 State Veterinarian, Lansing, Michigan.
5*. DRIVER, F. C. 1944 U. S. Department of Agriculture, St. Paul, Minnesota.
6*. FRY, H. L. 1951 U. S. Department of Agriculture, Nashville, Tennessee.
7*. GARRETT, H. U. 1951 Division Animal Industry, Des Moines, Iowa.
8*. GOOD, G. H. 1951 State Livestock and Sanitary Board, Cheyenne, Wyoming.
9*. GREEN, T. C. 1951 State Veterinarian, Charleston, West Virginia.
10*. HAHN, H. C. 1951 Texas Game Fish and Oyster Commission, Austin, Texas.
11*. HEINY, E. 1951 Denver, Colorado.
12*. JONES, T. J. 1951 University of Georgia, Athens, Georgia.
13*. LAUDERDALE, B. N. 1951 U. S. Department of Agriculture, Montgomery, Alabama.
14*. LAY, R. H. 1951 Health of Animals Division, Department of Agriculture, Winnipeg, Manitoba, Canada.
15*. LOZANO, E. 1952 University of Wisconsin, Madison, Wisconsin.
16*. LEASURE, E. F. 1951 Kansas State College, Manhattan, Kansas.
17*. LEE, W. R. 1951 U. S. Department of Agriculture, Phoenix, Arizona.
18*. LUQUE, G. F. 1951 Facultad de Medicina Veterinaria y de Zootechnia, Bogota, Colombia, South America.
19*. MCCALLAM, J. A. 1951 Chief, Vet. Div., Office Surgeon General, Washington, D. C.
20*. MELVIN, F. H. 1951 U. S. Department of Agriculture, Salt Lake City, Utah.
21*. MCERLEAN, B. 1951 Veterinarian Research Lab., Dublin, Eire.
22*. PISTOR, W. J. 1951 University of Arizona, Tucson, Arizona.
23*. RICKS, D. H. 1951 State Veterinarian, Oklahoma City, Oklahoma.
24*. ROBERTS, C. S. 1951 Livestock Sanitary Board, Auburn, Alabama.
25*. SCHOENING, H. W. 1951 U. S. Department of Agriculture, Washington, D. C.
26*. SCHNEIDER, A. P. 1951 State Bureau Animal Industry, Boise, Idaho.
27*. SCHNEIDER, F. L. 1951 Cattle Sanitary Board, Albuquerque, New Mexico.
28*. SHAHAN, M. S. 1951 U. S. Department of Agriculture, Washington, D. C.
29*. SMITH, L. H. 1951 U. S. Department of Agriculture, Denver, Colorado.
30*. WILKINS, H. F. 1951 Livestock Sanitary Board, Helena, Montana.